REMARKS

An Office Action was mailed in the above-captioned application on February 7, 2007. Claims 16, 18-20, 22, 24, 25, 29, and 53-58 were pending in the application. Claims 16, 18-20, 22, 24, 25, 29, and 53-58 were rejected. Claims 16, 20, 54, and 57 were objected to. This Amendment and Remarks document is submitted in response to said Office Action.

Specification

The Office action states that GenBank Accession numbers are used in Tables 1-2 and that the amino acid sequence is considered essential subject matter for assessing patentability of the instant invention. The Office action further states that different proteins may be referred to by different names and that accession numbers can change from time to time. The Office action also states that Applicant is required to amend the disclosure to include the material incorporated by reference.

It is unclear to Applicant what exact amendment is being asked for; clarification is requested.

To the extent that inclusion of actual sequences is requested, Applicant respectfully traverses this request. The Federal Circuit has held in *Capon v. Eshhar* (418 F.3d 1349 (Fed. Cir. 2005)) and *Falkner v. Inglis* (Fed. Cir. 2006, 05-1324) that where accessible literature sources clearly provided, as of the relevant date, for genes and their nucleotide sequences, satisfaction of the written description requirement does not require either the recitation or incorporation by reference of such genes and sequences. In the present application, both an accession number and a gi number are provided. The specification (paragraph [0052]) explains that the polypeptide markers are described by their corresponding identification number from NCBI's reference sequence database. An accession number is the unique identifier for a sequence record. An accession number applies to the complete record. Accession numbers do not change, even if information in the record is changed at the author's request. A gi number or "GenInfo Identifier" sequence identification number refers to a sequence identifier that runs parallel to the accession.version system. Therefore, if the protein sequence changes in any way, it will receive a new gi number. Thus, the combination of accession number and gi number

provides a clear and unambiguous source of the protein sequence as of the filing date. Such a description satisfies the written description requirement.

Claim Objections

Claims 16, 20, 22, 54, and 57 have been objected to as containing parentheses and it is allegedly unclear whether the recitations in parentheses are essential material necessary for the practice of the claim.

The protein designations in the claims are taken from the "Definition" field in the NCBI record for the protein at the time the application was filed. Copies of the NCBI records at the time of filing of the application are included for the Examiner's ease of reference. In order to clarify that the protein designation is a definition, the claims have been amended to place the entire protein definition in quotation marks.

Claims 24 and 29 have been objected to as containing the abbreviation "RA." Claims 24 and 29 have been amended to recite "rheumatoid arthritis" instead of "RA."

The Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Examiner has rejected claims 16, 19-20, 22, 24-25, 29 and 54 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). With this standard in mind, the rejection is discussed below.

The rejection states that the following phrases are indefinite: "hypothetical", "as similar to KIAA1902 Protein," and "reference value."

Regarding "hypothetical", and "as similar to KIAA1902 Protein," these phrases appear in the NCBI definitions for the proteins. As noted above, the claims have been amended to place the entire protein definition at the time the application was filed in quotation marks in order to clarify the claims. Thus, it is clear that the terms in quotation marks in the claims simply refer to the protein identified by the

Regarding the phrase "reference value," the rejection suggests that what is adequately described is a reference value from a healthy control. Applicant disagrees with this statement; however, solely in the interest of expediting prosecution, Claim 16 has been amended to recite a reference value from a healthy control or a reference value from an .

Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner has rejected claims 16, 18-20, 22, 24-25, 29 and 53-58 under 35 U.S.C. § 112, first paragraph for lacking enablement.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971).

Specifically, the rejection states that while the specification is enabling for a using healthy reference, it does not reasonably provide enablement for any reference. Applicant disagrees with this statement; however, solely in the interest of expediting prosecution, Claim 16 has been amended to recite a reference value from a healthy control.

The Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 16, 18-20, 22, 24-25, 29, and 53-58 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area that applicants regard as their invention with a *reasonable* degree of precision and particularity.

Specifically, the rejection states that the following recitations are indefinite: "hypothetical", "as similar to KIAA1902," "[Homo Sapiens]," "leucine-rich." As explained above, the protein designations in the claims are taken from the "Definition" field in NCBI's record for the protein. In order to clarify this, the claims have been amended to place the entire protein definition in quotation marks. It is believed that this amendment clarifies that the protein designation is a standard definition.

Claim 16 is rejected for use of the allegedly indefinite recitation "reference value." Although Applicant believes this term to be definite, Claim 16 has been amended to recite a reference value from a healthy control, solely in the interest of expediting prosecution.

Claim 24 has been rejected in that the recitations "the standard level" and "reference range" lack antecedent basis. Claim 24 has been amended to replace these recitations with the phrase "reference value."

Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 16, 18, 19, 20, 24, 25, 53 and 58 under 35 U.S.C. § 103(a) as being unpatentable. The Examiner bears the burden of establishing a prima facie case of obviousness (Section 103). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

A. Claims 16, 24-25, and 58. The Examiner has rejected Claims 16, 24-25 and 58 under 35 U.S.C. § 103(a) as being unpatentable over Winchester, et al., U.S. Patent Application Publication No. 2005-0202005 in view of Dwek, et al., U.S. Patent No. 4,659,659.

The rejection states that although the claims recite determining a plurality of markers, the claim can be interpreted using one marker for diagnosing rheumatoid arthritis. Claim 16 has been amended to recite determining the level of a one or more markers to clarify the invention.

The rejection also states the Winchester, et al., teach using biological samples from rheumatoid arthritis and osteoarthritis patients to determine the difference of gene expression within the two groups. The rejection further states that Winchester, et al., disclose that lumican protein is significantly overexpressed in rheumatoid arthritis patients compared to osteoarthritis patients, but that Winchester, et al., does not explicitly teach diagnosing rheumatoid arthritis.

The rejection states that Dwek, et al., teach measuring a marker, i.e., galactosylation of an IgG component or fragment thereof, from the plasma, serum or synovial fluid from rheumatoid

arthritis, osteoarthritis and normal subjects, that the populations have different levels of galactosylated IgG, and that these results can be used for diagnosis purposes. The rejection reasons that one skilled in the art would be motivated to measure the level of lumican protein in suspected rheumatoid arthritis patients as taught by Winchester, et al. because of the discrepancy of protein markers in rheumatoid arthritis and osteoarthritis.

Applicant respectfully traverses this rejection. Dwek, et al., teaches that osteoarthritis and rheumatoid arthritis are associated with changes in the level of outer-arm galactosylation of the complex N-linked oligosaccharides of total serum IgG. Dwek, et al., does not teach or suggest that other proteins be used to diagnose rheumatoid arthritis or osteoarthritis. Merely because the marker disclosed by Dwek, et al. (glycosylated IgG) is decreased in rheumatoid arthritis and osteoarthritis patients as compared to normal populations, there is no reason to assume that the same would happen with any other protein, including the lumican protein disclosed by Winchester, et al.

Winchester, et al. teaches a difference in lumican levels in cultured cells derived from rheumatoid arthritis and osteoarthritis patients. The use of lumican as a rheumatoid arthritis marker in a patient sample as compared to a reference from a healthy individual, as required by claim 16, is not taught or suggested, as explained in detail below.

Winchester, et al., studied cells originating from a rheumatoid arthritis patient that were repeatedly cultured to yield a cultured cell line with phenotypic alterations as compared to the parent cell. (paragraphs [0107]-[0108]). The resulting cells have a complex and not entirely uniform phenotype (paragraph [0109]). Thus, Winchester, et al., does not use a patient sample as required by Claim 16.

The reason for cultured cell phenotype(s) is not clear; however, Winchester, et al. states that one possibility for the distinctive phenotype "could be the normal phenotype of the fibroblast-like intimal synoviocyte found in the normal joints in all individuals." (paragraph [0114]). That is, Winchester, et al. suggests that lumican is not a marker for rheumatoid arthritis, but rather a protein present normally. Winchester, et al., conclude that:

> differential gene expression seen in cultured rheumatoid arthritis synovial fibroblast is lineage-dependent and related to the initial proportion of intimal mesenchymal stem-like to subintimal cells in the biopsy or surgical specimens, with the differential expression representing increased number, or hyperplasia, of intimal cells. Thus much of the distinctive phenotype of cultured rheumatoid arthritis synoviocytes could be a combination of the intrinsic pattern of gene

> expression in this stem cell-like sublineage and its pattern of response to culture *in vitro*. The pattern of gene expression seen in the fibroblast-like synoviocyte suggests that this cell may represent a form of less differentiated cell, closer to the mesenchymal stem-cell than to the typical fibroblast.

(paragraph [0182]). That is, Winchester, et al., does not conclude that lumican is a marker for rheumatoid arthritis, but rather, its presence in cultured cells can be accounted for by factors other than having rheumatoid arthritis. In this respect, Winchester, et al., teaches away from the present invention.

Dwek, et al., teaches that galactosylated IgG decreases in both rheumatoid arthritis and osteoarthritis. Dwek, et al., does not teach or suggest the use of markers other than galactosylated IgG, and therefore provides no motivation to search for other markers, let alone the specific marker of lumican. Thus, there is no motivation to combine Dwek, et al., with Winchester, et al.

Winchester, et al., using cultured cells having a phenotype altered from the original patient sample, teaches that lumican expression differs in cells derived from osteoarthritis patients and rheumatoid arthritis patients. Winchester, et al., suggests that lumican is not a marker for rheumatoid arthritis when using a normal reference value.

The combination of references (which applicants do not admit is proper) does not render the present claims obvious, since Winchester teaches away from using lumican as a marker for rheumatoid arthritis and does not teach using a patient sample or reference value from a healthy control, as required by Claim 16, 24, 25, and 58.

B. Claims 16, 18, 19 and 53. The Examiner has rejected Claims 16, 18, 19 and 53 under 35 U.S.C. § 103(a) as being unpatentable and over Chard, et al., *Annals of Rheumatic Diseases* 1988 47:665-71, in view of Dwek, et al., U.S. Patent No. 4,659,659 and further in view of Winchester, et al., U.S. Patent Application Publication No. 2005-0202005.

The rejection states that Chard, et al., teach a method of assessing rheumatoid arthritis patients by detection of a plurality of biomarkers, including alpha-1-antichymotrypsin (ACT), show that serum concentration of ACT correlates with the activity of rheumatoid arthritis, but that Chard, et al., does not teach comparing the level of serum ACT to a reference value. The rejection reiterates the teachings of Dwek, et al., as stated above. The rejection reasons that one skilled in the art would be motivated to measure the level of ACT in rheumatoid arthritis patients

as taught by Chard, et al. with comparison to a reference value as taught by Dwek, et al, for the purpose of diagnosis.

Applicants do not acquiesce in this rejection; however, in the interest of expediting prosecution, Claim 16 has been amended to delete the recitation "a polypeptide marker identified as Alpha-1-antichymotrypsin precursor (ACT)" and Claim 53 has been cancelled. It is believed that the amendment overcomes the rejection.

C. Claim 20. The Examiner has rejected Claim 20 under 35 U.S.C. § 103(a) as being unpatentable and over Chard, et al., *Annals of Rheumatic Diseases* 1988 47:665-71, in view of Dwek, et al., U.S. Patent No. 4,659,659.

The rejection reasons that it would have been obvious to combine measuring two markers such as lumican and ACT as taught by Winchester and Chard, et al., and comparing to a reference as taught by Dwek, et al. for diagnosis because using lumican and ACT were found to be an effective biomarkers, and using a plurality of markers is taught by Chard, et al.

Applicants do not acquiesce in this rejection; however, in the interest of expediting prosecution, Claim 20 has been amended to delete the recitation "a polypeptide marker identified as Alpha-1-antichymotrypsin precursor (ACT)" and Claim 53 has been cancelled. It is believed that the amendment overcomes the rejection.

In view of the foregoing amendments and arguments, reconsideration of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The

undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

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